

State model for partly undetected non-communicable diseases (NCDs)

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Abstract

This article proposes an age-structured compartment model for irreversible diseases with a pre-clinical state of undiagnosed cases that precedes the diagnosis. The model is able to cope with mortality rates differing between the pre-clinical and the clinical state (differential mortality). Applicability is tested in a hypothetical disease with realistic incidence and mortality rates.

1 Introduction

Many non-communicable diseases (NCDs) progress unobserved before clinical symptoms occur. Examples are certain types of cancer [Lao13], diabetes [Bea14] and dementia [Hod11]. Mostly, reasons for the undetected progression may be the lack of early symptoms. Other reasons are missing awareness of patients and physicians, lack of practical diagnostic tests or incoherent definitions for a diagnosis of the disease. In some cases, the progressing condition may be completely unknown.

The next section introduces a compartment model with a pre-clinical stage preceding the clinical stage. As in the field of infectious disease epidemiology we describe the disease dynamics of a population by differential equations involving the transition rates between the compartments [Vyn10]. The model described here is able to cope with secular trends, i.e. involves calendar time t , and the different ages a of the subjects in the population. Sometimes these models are called *age-structured*.

Although considering a pre-clinical state preceding a diagnosis is at least going back to 1969 [Zel69] and a considerable amount of work has been devoted

to compartment models since then, to our knowledge a description using differential equations in calendar time t and age a is new. Furthermore, other models distinguish between disease-specific mortalities and other causes of death (e.g. [Tol78]). However, we consider this approach critical, because there might be cases where the cause of death is not clearly attributable. Is a death by an infection (say pneumonia) due to the disease (e.g. the immunosuppressive treatment in cancer) or is it independent from the disease? In practical cases this is difficult to judge.

In the third section the compartment model is used in an example of an partly unobserved disease. We mimic the situation that a hypothetical population suffers from a fictional NCD that is detected at a certain point in time. From that time on, the medical community is aware, starts to diagnose and treat the newly discovered condition.

2 Diagnosis Model

In modelling chronic (irreversible) diseases, often the three-state model (compartment model) in Figure 1 is used. The numbers of persons in the states *Normal*, *Undiagnosed* and *Diagnosed* are denoted by S, U , and C . The transition intensities (synonym: rates) between the states are: the incidence rates λ_0, λ_1 and the mortality rates μ_0, μ_1 and μ_2 . These rates generally depend on the calendar time t and the age a .

Although the inclusion of the disease duration d is also possible [Bri13], hereinafter it is assumed that m_1 does not depend on d . Analogously to [Bri12b], we look for the numbers $S(t, a), U(t, a)$ and $C(t, a)$ of healthy, undiagnosed and diagnosed persons in terms of differential equations, which can be derived from the disease model in Figure 1. For the healthy persons we get the following initial value problem of Cauchy type:

$$(1) \quad \begin{aligned} (\partial_t + \partial_a) S(t, a) &= -(\mu_0(t, a) + \lambda_0(t, a)) S(t, a) \\ S(t, 0) &= S_0(t). \end{aligned}$$

Here $S_0(t)$ is the number of (healthy) newborns¹ at calendar time t . The notation ∂_x denotes the partial derivative with respect to x , $x \in \{t, a\}$.

The numbers U and C of diseased persons without and with diagnosis are

¹Here we just consider diseases contracted after birth.

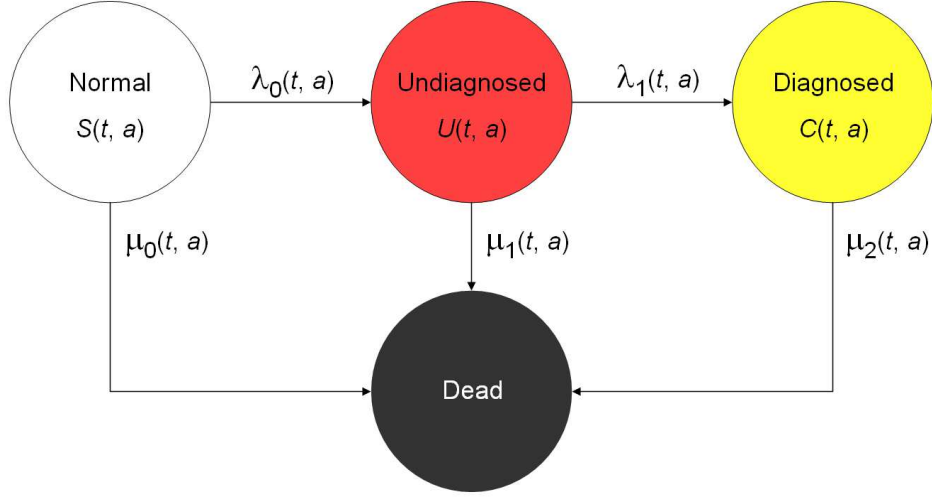


Figure 1: Chronic disease model with four states and the corresponding transition rates. People in the state *Normal* are healthy with respect to the disease under consideration. After onset of the disease, they change to state *Undiagnosed* and later to the state *D*. The absorbing state *Dead* can be reached from all other states. The numbers of persons in the states and the transition rates depend on calendar time t and age a .

described similarly:

$$(2) \quad (\partial_t + \partial_a) U(t, a) = -(\mu_1(t, a) + \lambda_1(t, a)) U(t, a) + \lambda_0(t, a) S(t, a) \\ U(t, 0) = 0.$$

$$(3) \quad (\partial_t + \partial_a) C(t, a) = -\mu_2(t, a) C(t, a) + \lambda_1(t, a) U(t, a) \\ C(t, 0) = 0.$$

After defining $N(t, a) = S(t, a) + U(t, a) + C(t, a)$ and

$$p_0(t, a) = S(t, a)/N(t, a) \\ p_1(t, a) = U(t, a)/N(t, a) \\ p_2(t, a) = C(t, a)/N(t, a),$$

the overall mortality (general mortality) μ in the population may be written as

$$\mu = p_0 \mu_0 + p_1 \mu_1 + p_2 \mu_2.$$

By using $p_0 + p_1 + p_2 = 1$, the partial differential equations (2) and (3) read as

$$\begin{aligned}
(4) \quad & (\partial_t + \partial_a)p_1 = -(\lambda_0 + \lambda_1 + \mu_1 - \mu)p_1 - \lambda_0 p_2 + \lambda_0 \\
(5) \quad & (\partial_t + \partial_a)p_2 = \lambda_1 p_1 - (\mu_2 - \mu)p_2.
\end{aligned}$$

Together with the initial conditions $p_1(t, 0) = p_2(t, 0) = 0$ for all t , the system (4) - (5) completely describes the dynamics of the disease in the considered population. The values of p_0 are obtained by using $p_0 = 1 - p_1 - p_2$. Note that the system (4) - (5) does not explicitly depend on the mortality of the healthy subjects μ_0 , which is typically unknown. The remaining rates $(\lambda_0, \lambda_1, \mu_1, \mu_2)$ are either accessible by (specially designed) epidemiological studies or by official vital statistics (μ).

3 Simulation

We use system (4) - (5) to describe a hypothetical irreversible disease, which is undiagnosed until a specific point in time t^* . At t^* the disease is detected and diagnosed henceforth. As a consequence, after t^* the prevalence p_1 of undetected cases decreases whereas the prevalence p_2 of detected cases increases. The general mortality μ is chosen as the (approximated) general mortality of the German male population in from 1900 ($t = 0$) to 2010 ($t = 110$:)

$$\mu(t, a) = \exp(\beta_0(t) + \beta_1(t) a),$$

with $\beta_0(t) = -7.078 - 0.02592 t$ and $\beta_1(t) = 0.06401 + 2.455 \cdot 10^{-4} t$. For simplicity, the mortality rates μ_ℓ , $\ell = 1, 2$, are assumed to be proportional to μ : $\mu_1 = 3.5 \mu$ and $\mu_2 = 2.5 \mu$. The factor for μ_1 is chosen to be larger than the one for μ_2 , because in contrast to the persons in the *detected* state the persons in the *undetected* state cannot be treated for the disease.

The rates $\lambda_\ell, \ell = 0, 1$, are modified incidence rates of dementia in German males [Zie09]. The rate λ_0 is the 1.5-fold rate of the values in [Zie09], which mimics one undetected case per two detected cases for $t \geq 75$, see Table 1. For year $t = 75$ the rates λ_1 are also shown in Table 1. There is a secular trend in λ_1 mimicking the increasing awareness for the disease. In the simulation, λ_1 increases by 1 % per year for all ages a .

If we solve the system (4) - (5) by the methods of characteristics, we obtain the prevalences of the undiagnosed and diagnosed disease as shown in Figures 2 and 3, respectively. The qualitative change after 1975 ($t = 75$) in both prevalences p_1 and p_2 is clearly visible in the upper right corner of the figures. For better comparison, the age-specific prevalences in 1970 ($t = 70$) and 1980 ($t = 80$) are additionally shown in Figure 4. In 1970, there are no diagnosed

Age (years)	Incidence λ_0 (per 100 person-years)	Incidence λ_1 in the year 75 (per 100 person-years)
≤ 62.5	0	0
67.5	0.3	3.3
72.5	0.7	7.8
77.5	1.7	20
82.5	3.0	33
87.5	5.2	58
92.5	7.6	510
97.5	9.9	1340
≥ 100	11.2	4110

Table 1: Age-specific incidence rates λ_0 and λ_1 . For the $t > 75$ the rate λ_1 increases by 1% annually for all ages.

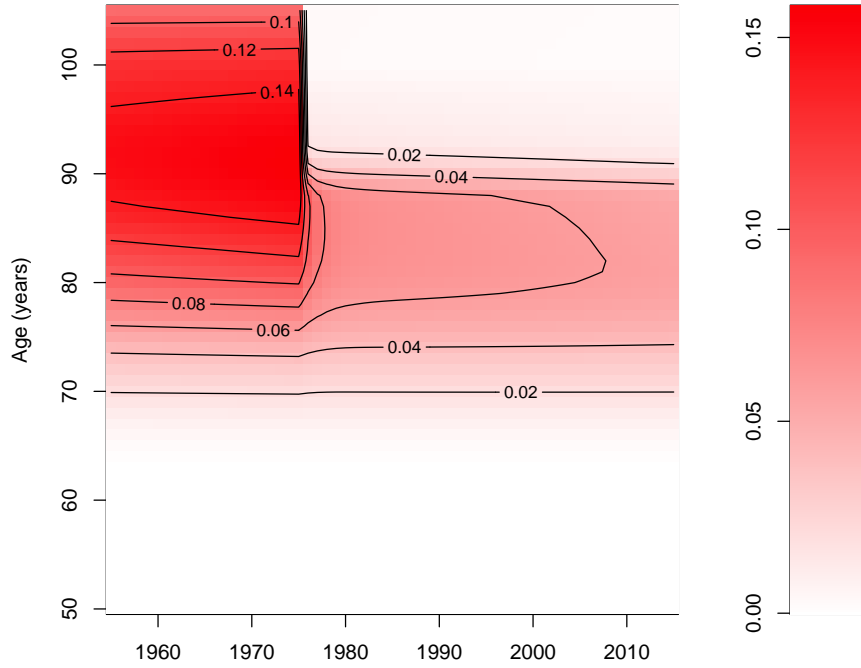


Figure 2: Prevalence of the undiagnosed disease (p_1) over year and age (left). The colour corresponds to value of the prevalence (coding scheme on the right hand side).

cases (the hypothetical disease is not detected yet). The prevalence of the undiagnosed cases (p_1) is peaking at about 16% at the age of 91 years. Ten

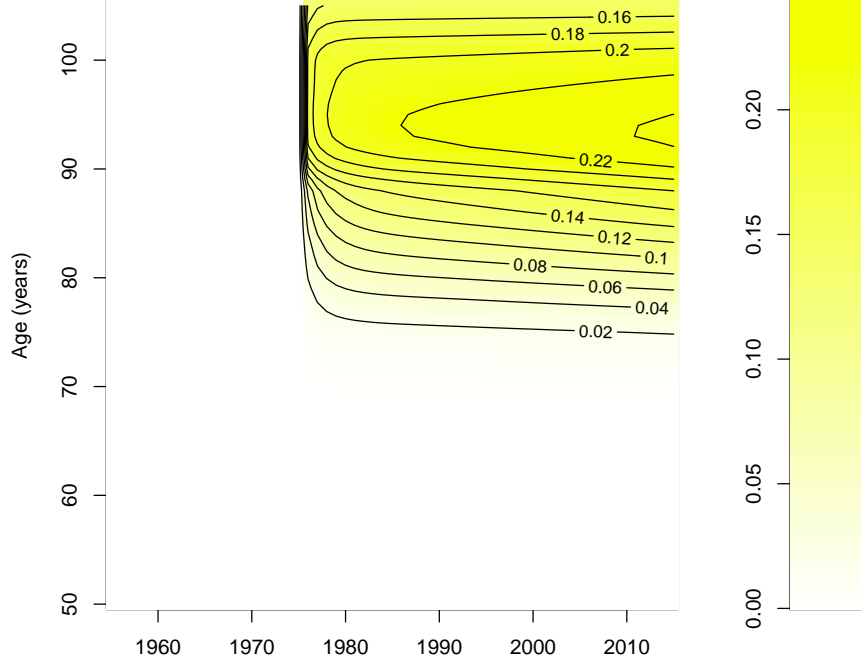


Figure 3: Prevalence of the diagnosed disease (p_2) over year and age (left). The colour corresponds to the value of prevalence (coding scheme on the right hand side).

years later, the disease has been detected and the medical community is making diagnoses. Hence, the prevalence of the undiagnosed disease has tremendously decreased – to less than 8%. Especially in the higher age groups (≥ 95) the physicians are aware and detect a high proportion of cases. Thus, the prevalence of diagnosed cases (p_2) has increased a lot.

It is amazing, how much the overall prevalence ($p_1 + p_2$) in 1970 differs from the one in 1980 (cf. Figure 5). This is an effect of the lowered mortality for those diseased persons who have been detected (and are treated since then). Since the mortality μ_2 is much lower than μ_1 , the overall survival of the diseased persons is improved after 1975 and the overall prevalence increases.

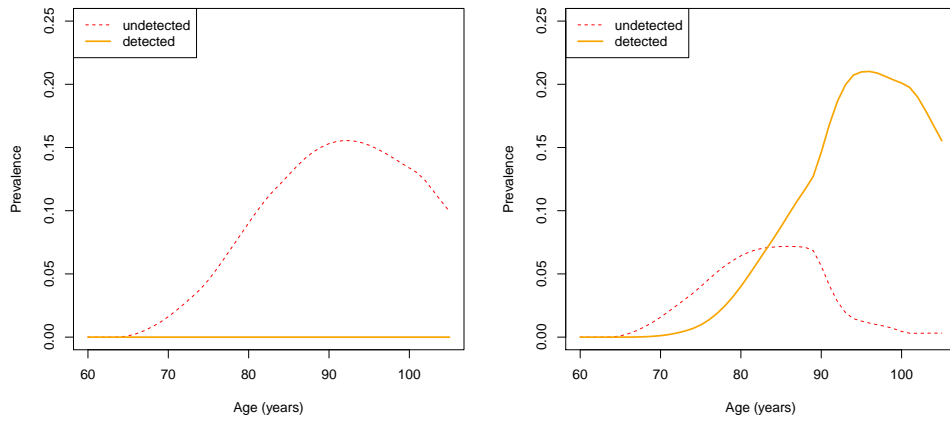


Figure 4: Age-specific prevalence of the undiagnosed (red, dashed lines) and the diagnosed disease (orange, solid lines) in 1970 ($t = 70$, left) and in 1980 ($t = 80$, right).

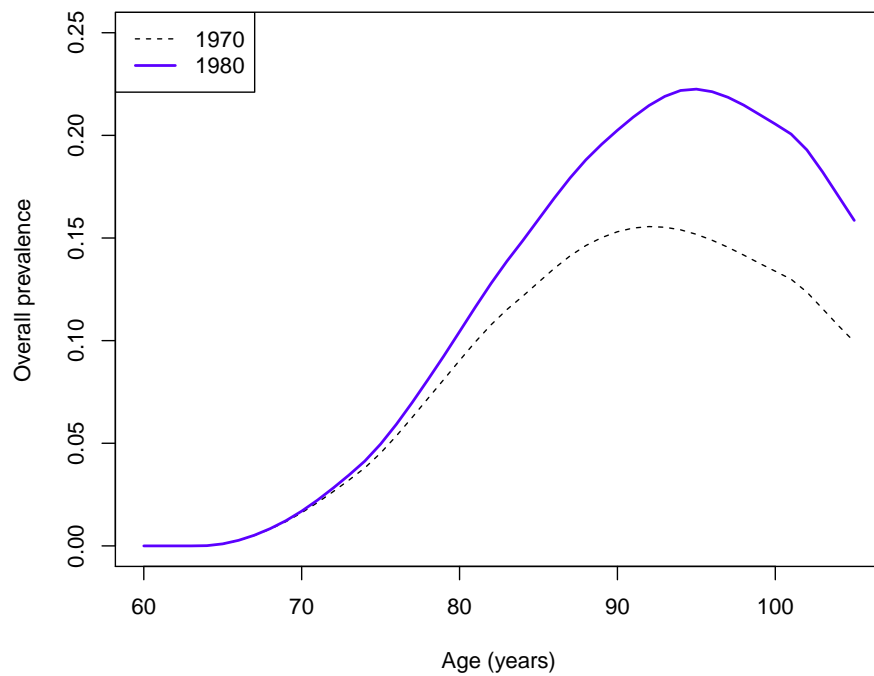


Figure 5: Overall age-specific prevalence ($p_1 + p_2$) in 1970 (black dashed line) and in 1980 (blue solid line).

4 Discussion

In this work, a novel approach for analysing epidemiological measures of a chronic disease is proposed. With a view to the chronic (incurable) disease, a pre-clinical state is considered in which the disease is at least partly undiagnosed. The situation is described in an age-structured compartment model using a set of partial differential equations.

There are various chronic diseases that have an pre-clinical state preceding a diagnosis. Examples were given in the introductory section of this article. Other diseases with an asymptomatic pre-clinical state are chronic kidney disease (CKD), hypertension and arteriosclerosis.

So far, we just considered non-communicable diseases. However some incurable infectious diseases, such as HIV or hepatitis C, also have an asymptomatic pre-clinical phase. Thus, the compartment model of Figure 1 as well may be useful in these cases.

In an example we have demonstrated the applicability of the modelling framework for a hypothetical chronic disease that has been detected at a specific point in time and has been diagnosed and treated since then. Examples analogue to the one shown may give insight about the ratio between undiagnosed and diagnosed cases in a chronic disease.

A final remark about the system (4) - (5) and the example: Since the transition rates for the compartment model are assumed to be known, we speak of a *forward problem* [Bri12a]. There is an associated *inverse problem*, which might be interesting.

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